T-cell replete haploidentical stem cell transplantation attenuates the prognostic impact of FLT3-ITD in acute myeloid leukemia. A report from the Acute Leukemia Working Party of the EBMT

Haploidentical stem cell transplantation abrogates the prognostic impact of *FLT3-ITD* in acute myeloid leukemia. A report from the Acute Leukemia Working Party of the EBMT.

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Disclaimers

None

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Abstract (265)

Purpose

Acute myeloid leukemia (AML) patients harboring the Fms-like tyrosine kinase 3 internal tandem duplication (*FLT3-ITD*) mutation are considered a particularly high risk patient subset preferentially allocated for allogeneic stem cell transplantation in first remission. Whether *FLT3-ITD* retains a prognostic role in haploidentical stem cell transplantation (haplo-SCT) is currently unknown.

Patients and methods

Using the international multicenter registry of the acute leukemia working party of the European society for blood and marrow transplantation, we performed a retrospective analysis to determine whether *FLT3-ITD* was prognostically significant in T-cell replete haplo-SCT transplanted AML patients.

Results

We evaluated 293 de-novo AML patients (202 $FLT3^{wt}$ and 91 $FLT3\text{-}ITD^{mut}$) transplanted in first remission with T-cell replete haplo-SCT between 2005-2016. $FLT3\text{-}ITD^{mut}$ patients were more likely to be *NPM1* mutated as well as be in the intermediate risk cytogenetic risk category. In multivariate analysis, patients with *FLT3-ITD* had comparable rates of relapse incidence [Hazard ratio (HR)=1.34, confidence interval (CI) 95%, 0.67–2.7; P=0.9] and leukemia-free survival (HR=0.99, CI 95%, 0.62–1.57; P=0.9) to those of $FLT3^{wt}$ patients. Survival was not significantly impacted by *FLT3-ITD* status (HR=0.96, CI 95%, 0.58–1.59; P=0.8), nor were the incidence of non-relapse mortality (HR=0.78, CI 95%, 0.41–1.46; P=0.44), and graft versus host disease-free/relapse-free survival (HR=0.84, CI 95%, 0.54–1.28; P=0.42). Focused subset analysis of patients with intermediate risk cytogenetics confirmed the absence of a prognostic impact of *FLT3-ITD* also for this group of patients.

Conclusion

In AML patients undergoing T-cell replete haplo-SCT, the *FLT3-ITD* mutation does not retain its prognostic significance, potentially indicative of haplo-SCT's capacity to overcome the negative prognostic consequences of *FLT3-ITD* in AML.

Introduction

Acute myeloid leukemia (AML) patients harboring the Fms-like tyrosine kinase 3 internal tandem duplication (*FLT3-ITD*) mutation are a particularly clinically challenging patient segment in the field of hematologic malignancies. Nearly a third of AML patients with baseline normal cytogenetics present with *FLT3-ITD* which has consistently been shown to confer poor long term outcomes resulting from a remarkably high relapse rate[1-8]. Whereas the negative prognostic impact imparted by *FLT3-ITD* is unequivocal, an ongoing debate in the field revolves around the question of whether allogeneic stem cell transplantation can overcome the detrimental impact of *FLT3-ITD*. In contrast to earlier published data[9], and notwithstanding the paucity of randomized trials comparing transplantation with chemotherapy exclusive approaches, the bulk of current evidence suggests that allogeneic transplantation improves survival of *FLT-ITD* mutated patients[7,10-15]. Haploidentical stem cell transplantation (haplo-SCT) presents a valid option for those patients in need of allogeneic transplantation and lacking a fully matched HLA matched donor. The early experience with haplo-SCT was initially characterized by an increased incidence of transplant related mortality due to the slow kinetics of immune reconstitution leading to an increased incidence of fungal and viral infections as well as graft rejection[16]. However, significant advances in haplo-SCT have been recently realized with the introduction of novel immunosuppression modulation approaches, namely post-transplantation cyclophosphamide (PTCy)[17] and anti-thymocyte globulin (ATG) based protocols[18], which via selective in-vivo depletion of donor T cells have achieved acceptable rates of engraftment, thus negating the need for profound T cell depletion. Indeed, the evolving application of haplo-SCT in AML is evident with recent publications indicating comparable clinical outcomes between allogeneic transplantation from partially HLA mismatched (9/10) unrelated donors, and possibly HLA matched unrelated (10/10) donors and even HLA matched sibling donors to those of haplo-SCT[19-24], and therefore it is becoming imperative to characterize the impact of haplo-SCT on specific subsets of AML patients. As of yet, no formal evaluation of the impact of *FLT3-ITD* on outcomes following haplo-SCT has been performed. In this analysis of 293 AML patients, we set out to determine whether *FLT3-ITD* maintained its prognostic significance for AML patients undergoing T-cell replete haplo-HCT in first remission.

Methods

Study Design and Data Collection

This analysis was a retrospective multicenter analysis performed by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The latter is a voluntary working group comprising more than 500 transplant centers required to report on an annual basis on all transplants performed. Quality control measures of the multicenter registry include confirmation of the validity of the entered data by the reporting team, cross-checking with the national registries, and regular in-house and external data audits.

Patients included in this analysis were adult de-novo AML patients, over the age of 18, undergoing a first T-cell replete related haplo-HCT from 2005 through 2016 while in first complete remission. This study was approved by the ALWP institutional review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent authorizing the use of their personal information for research purposes. The list of participating centers is available in the supplementary appendix.

Statistical Analysis

Clinical outcomes were evaluated as follows: (I) non-relapse mortality (NRM), defined as death without previous relapse; (II) relapse incidence (RI), defined on the basis of morphological evidence of leukemia in bone marrow or other extramedullary organs; (III) leukemia-free survival (LFS), defined as the time from transplantation to first event (either relapse or death in complete remission); (IV) GVHD-free/relapse-free survival (GRFS), defined as events including grade 3-4 acute GVHD, extensive chronic GVHD, relapse, or death in the first post-HCT year[25]; and (V) overall survival. Cumulative incidence curves were used for RI and NRM in a competing risks setting, since death and relapse are competing. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier estimate. The probabilities of NRM, RI, acute and chronic GVHD were calculated using the cumulative incidence estimator to accommodate for competing risks[26]. Univariate analyses were done using the Gray's test for cumulative incidence functions and the log rank test for OS, GRFS, and LFS. A Cox proportional hazards model was used for multivariate regression. Variables included in multivariate models were either with unbalanced distribution or potential impact on outcome. Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). Proportional hazards assumptions were checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All tests were 2-sided. The type 1 error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS 22.0 (SPSS Inc, Chicago, IL, USA) and R 3.2.3 (R Development Core Team, Vienna, Austria) software packages.

Results

Patient, disease and transplant baseline characteristics

The analyzed cohort comprised 293 patients transplanted between 2005-2016, 91 of whom were *FLT3-ITD* mutated. As summarized in table 1, compared to *FLT3*^{wt}, the group of *FLT3-ITD* mutated patients did not differ to a significant degree with respect to patient age, donor age, performance status, and CMV donor-recipient matching. *FLT3-ITD*^{mut} patients were more likely to have ELN intermediate risk cytogenetics whereas poor risk cytogenetics were more frequently seen in *FLT3*^{wt} patients. Additionally, most of the *FLT3-ITD*^{mut} patients had a concomitant *NPM1*

mutation while the majority of *FLT3-ITD*^{wt} patients did not have an *NPM1* mutation (61% versus 10%; *P*=0.0001). Conditioning intensity did not differ to a significant degree between *FLT3-ITD* mutated patients and *FLT3*^{wt} patients; supplementary table 1 outlines the various conditioning regimens used for patients in this analysis.

Transplant outcomes

Neutrophil recovery rates at 30 days were not significantly different between *FLT3-ITD*^{mut} and *FLT3*^{wt} patients with a 96% engraftment rate observed in both groups; *P*=0.9. At 2 years, the incidence of relapse was 17% (95% CI: 12.6-22) with a 61% (95% CI: 55.1-67.4) rate of leukemia-free survival. The overall survival rate was 66% (95% CI: 60.8-72.8) whereas non-relapse mortality was seen in 21% of the patients on this cohort (95% CI: 16.9-27). Grade II-IV acute GHVD was experienced by 29% (95% CI: 24-34.6) of the patients while chronic GVHD was diagnosed in 36% (95% CI: 30.1-42.4) of patients. Extensive chronic GVHD was seen in 11% of the patients (95% CI: 8.1-16.4). Supplementary table 2 outlines the main etiologies accounting for patient death in this analysis, with lethal infections and disease relapse being the leading causes for patient death.

Impact of *FLT3-ITD* on clinical outcome

To determine whether *FLT3-ITD* impacted on clinical outcome, we initially performed a univariate analysis which is summarized in table 2 and figure 1. Harboring *FLT3-ITD* did not significantly influence disease related clinical outcomes, namely relapse incidence (24% versus 14%, *P*=0.1) and leukemia-free survival (55% versus 63%, *P*=0.49), nor did it affect in a statistically significant manner transplant related outcomes such as non-relapse mortality (20% versus 22%, *P*=0.62), acute and chronic graft versus host disease, and GVHD-free/relapse-free survival (49% versus 50%, *P*=0.79). Overall survival was also not impacted by the mutational status of *FLT3-ITD* (65% versus 67%, *P*=0.88). Notably, the presence or absence of a concomitant *NPM1* mutation also did not influence clinical outcome in a statistically meaningful way. To assess whether the specific immunomodulation approach employed differentially affected outcome, a univariate analysis was carried out analyzing the outcomes of *FLT3-ITD* patients versus *FLT3*^{wt} in ATG and PTCy treated patients. As shown in supplementary table 3, both in PTCy and ATG treated patients, *FLT3-ITD* status did not influence outcome in a statistically significant way. Finally, a multivariate analysis was carried out which as depicted in table 3, confirmed that *FLT3-ITD* mutational status did not significantly affect clinical and transplant related outcomes.

Impact of *FLT3-ITD* on outcome of patients with intermediate risk cytogenetics

Since most of the *FLT3-ITD* patients were in the ELN intermediate risk cytogenetics category, we repeated our analysis focusing specifically on the 210 patients with intermediate risk cytogenetics. In this subgroup analysis, whose baseline data are summarized in supplementary 4, patients not harboring the *FLT3-ITD* mutation were younger (39 versus 45; *P*=0.023), and were

less likely to be given PTCy compared to their *FLT3-ITD* mutated counterparts (38% versus 55%; *P*=0.004). For this group of patients the 2 year leukemia-free survival and overall survival rates were 59% and 66%, respectively, whereas relapse incidence and non-relapse mortality rates were 17% and 28%, respectively. Grade II-IV acute GVHD was observed in 28% of patients and chronic GVHD was diagnosed in 36%. As shown in figure 2, a univariate analysis followed by a multivariate analysis, summarized in table 4, confirmed that also for this group of patients, the presence of a *FLT3-ITD* mutation also did not influence disease or transplant related outcomes.

Discussion

Consequent to its high incidence and decidedly detrimental impact on patients, *FLT3-ITD* is considered the most important molecular determinant of outcome in AML patients. Thus, *FLT3-ITD* patients are referred to transplant early during the therapeutic sequence with the hope that allogeneic stem cell transplantation will mitigate some of the unfavorable clinical magnitude associated with *FLT3-ITD*[27,28]. In this analysis we attempted to determine whether in AML patients undergoing haplo-SCT, *FLT3-ITD* is still clinically meaningful following transplant. The results of our analysis show that outcomes of haplo transplanted AML patients were not significantly affected by *FLT3-ITD*$^+$ status, thus challenging the notion that *FLT3-ITD* retains its negative impact even following allogeneic transplantation.

The impact and justification for allogeneic SCT in *FLT3-ITD* AML has been extensively investigated in the last decade. It is now firmly accepted that *FLT3-ITD* patients treated with chemotherapy alone stand a very poor chance of long term survival resulting from reported relapse rates of over 70%[1-4,6,9,29]. Accordingly, the standard of care for these patients is transplantation in first remission[30,31]. Whereas most publications in the field support a beneficial role for allogeneic SCT in the setting of *FLT3-ITD*$^+$ AML[7,11-14,32], we note a recently published CIBMTR analysis of 511 AML patients demonstrating that while *FLT3* mutated patients had increased relapse incidence compared with patients without the mutation, the 3 year leukemia-free survival and overall survival rates were not significantly different for both groups[33].

The emerging experience with haplo-SCT in AML is suggestive of a comparable degree of disease control with that of conventional stem cell sources, namely HLA matched sibling and unrelated donors[19-22]. Yet, to date the impact of *FLT3-ITD* in the setting of haplo-SCT has not been rigorously investigated. Our data indicate that the lack of a prognostic effect of *FLT3-ITD*, findings which diverge from the results of the recent analysis published by Wang and colleagues[22], where *FLT3-ITD* was found to be associated with a decreased 3 year disease free survival rate compared with non *FLT3-ITD* mutated patients (60% versus 79%). However, as most patients in that analysis did not have *FLT3-ITD* testing performed, interpretation of these data are to some extent limited. Our clinical outcomes are generally in line with the abovementioned studies examining the role of haplo-SCT in AML, with the inherent limitation of different time points analyzed, thus further strengthening the generalizability of our findings. Why haplo-SCT would render *FLT3-ITD* a less precarious determinant of clinical outcome and harbinger of relapse in AML is not fully clear. A possible explanation to consider may stem from

the markedly different immunological milieu encountered with the PTCy approach, namely the subsistence of quiescent progenitor cells and memory cells without the subset of alloreactive T-cells[16], which may consequently modulate the graft versus leukemia effect, possibly abrogating the detrimental effect of *FLT3-ITD* in terms of relapse incidence[34]. Moreover, it is conceivable that the limited use of immunosuppression after haplo-SCT, afforded by using PTCy which as noted earlier selectively depletes alloreactive T-cells while preserving anti leukemia T-cell subsets and NK cells, results in an increased graft versus leukemia effect[35]. Our data suggest that also for ATG treated patients, *FLT3-ITD* does not retain its prognostic significance which may be possibly accounted by an anti-leukemia effect of ATG as suggested by previously published registry data from China suggesting that in high risk acute leukemia patients, haplo-SCT with ATG prophylaxis resulted in lower leukemia relapse rates[36]. Further, recently published *in-vitro* data indicates that ATG may have intrinsic anti-leukemia activity[37].

Several important limitations to our analysis merit acknowledgement. As our knowledge of the molecular workings of AML expands, it is becoming clearly established that gene-gene interactions profoundly impact on the outcome of AML patients[38,39], thus the presence of *DNMT3A*, *IDH1*, *RUNX1*, and additional modifying genes which were not captured in our registry may have contributed to our findings. The *FLT3* allelic ratio is an additional prognostic component previously proposed to influence outcome of patients and which owing to the retrospective nature of dataset was not analyzed by us[32,40,41]. Finally, minimal residual disease (MRD) is increasingly being used to determine the depth of remission prior to stem cell transplantation and would decidedly further inform our analysis[42].

Taken together, the collective data in this analysis suggest that T cell replete haploidentical transplantation may conceivably mitigate the deleterious impact associated with *FLT3-ITD* in AML. Possible implications of our data are that T cell replete haplo-SCT may be a preferred therapeutic modality for this specific high risk subset of patients, a hypothesis that would need to be rigorously confirmed in randomized fashion.

Figure legends:

Figure 1. Clinical and transplant related outcomes of patients transplanted in first remission according to *FLT3-ITD* mutational status.

A- RI

B- LFS

C- NRM

D- OS

E- Acute GVHD

F- Chronic GVHD

Figure 2. Clinical and transplant related outcomes of intermediate risk patients transplanted in first remission according to *FLT3-ITD* mutational status.

A- RI

B- LFS

C- NRM

D- OS

E- Acute GVHD

F- Chronic GVHD

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